The neural crest-enriched microRNA miR-452 regulates epithelial-mesenchymal signaling in the first pharyngeal arch.

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Public Summary:
Neural crest cells (NCCs) are a subset of migratory stem cells that have the potential to give rise to cells from multiple lineages and populate a large number of tissues during development. NCCs are important for craniofacial and cardiac development. Although microRNAs (miRNAs) have emerged as important regulators of development and disease, little is known about their role in NCC development. Here, we show that mouse embryos that have a mutation that disrupts an enzyme called Dicer, required for miRNA formation, lack craniofacial cartilaginous structures and cardiac outflow tract septation. They also show inhibited development of certain types of neurons and the thymus gland, both derived from NCCs. Dicer mutant embryos had reduced expression of Dlx2, a protein that regulates development of the pharyngeal arches, which are structures in the embryo that eventually grow into parts of the face, throat, and heart. When a miRNA called miR-452 was enriched in NCCs, it reversed Dlx2 expression in Dicer mutant pharyngeal arches and regulated certain signaling pathways affecting the pharyngeal arches. Correspondingly, when miR-452 was removed from the NCCs, Dlx2 expression decreased, leading to craniofacial defects. These results suggest that miRNAs can regulate the process of differentiation of NCC-derived tissues and that miR-452 is involved in signaling in the pharyngeal arch between two different types of tissues, the epithelial tissues, which line cavities and surfaces of structures throughout the body, and the mesenchymal tissues, which are a type of connective tissue.

Scientific Abstract:
Neural crest cells (NCCs) are a subset of multipotent, migratory stem cells that populate a large number of tissues during development and are important for craniofacial and cardiac morphogenesis. Although microRNAs (miRNAs) have emerged as important regulators of development and disease, little is known about their role in NCC development. Here, we show that loss of miRNA biogenesis by NCC-specific disruption of murine Dicer results in embryos lacking craniofacial cartilaginous structures, cardiac outflow tract septation and thymic and dorsal root ganglia development. Dicer mutant embryos had reduced expression of Dlx2, a transcriptional regulator of pharyngeal arch development, in the first pharyngeal arch (PA1). miR-452 was enriched in NCCs, was sufficient to rescue Dlx2 expression in Dicer mutant pharyngeal arches, and regulated non-cell-autonomous signaling involving Wnt5a, Shh and Fgf8 that converged on Dlx2 regulation in PA1. Correspondingly, knockdown of miR-452 in vivo decreased Dlx2 expression in the mandibular component of PA1, leading to craniofacial defects. These results suggest that post-transcriptional regulation by miRNAs is required for differentiation of NCC-derived tissues and that miR-452 is involved in epithelial-mesenchymal signaling in the pharyngeal arch.